September 13, 2001

MEMORANDUM:

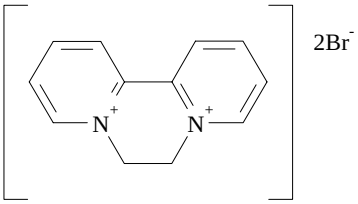
SUBJECT: **Diquat** (032201): Issues Pertaining to the Nature of the Residue in Plants, Animals and Water to be presented to the HED Metabolism Assessment Review Committee on September 25, 2001. **DP Barcode #** D277764. **Case 0288.**

FROM: Thurston G. Morton, Chemist
Reregistration Branch 4
Health Effects Division (7509C)

THROUGH: Susan V. Hummel, Branch Senior Scientist
Reregistration Branch 4
Health Effects Division (7509C)

TO: Metabolism Assessment Review Committee
Health Effects Division (7509C)

Diquat dibromide (6,7-dihydrodipyrido(1,2-a:2', 1'-c)pyrazinediium dibromide) is a non-selective contact herbicide, desiccant, and plant growth regulator primarily registered as a general herbicide for the control of broadleaf and grassy weeds on terrestrial non-crop and aquatic areas. Diquat dibromide is also registered as a preharvest desiccant in potato and crops grown for seed including alfalfa, carrot, clover, radish, sorghum, soybean, and turnip. Special local need registrations have been granted for the use of diquat dibromide as a postharvest desiccant on cantaloupe, cucumber, pepper, squash, tomato, and watermelon. The registered uses of diquat dibromide (i) as a preharvest desiccant on carrot, radish, and turnip grown for seed, and (ii) as a postharvest desiccant on cantaloupe, cucumber, pepper, squash, tomato, and watermelon are considered to be non-food uses. The diquat dibromide formulations registered for use on aquatic areas and food/feed crops are the 0.2 and 2 lb cation/gal soluble concentrate/liquid (SC/L). On crops, these formulations may be applied as preplant or preemergence broadcast applications or as preharvest/postharvest desiccants using ground or aerial equipment. On noncrop aquatic areas, the formulations registered may be applied as surface, sub-surface, or bottom placement treatments



Diquat dibromide

Summary of Plant and Livestock Metabolism Studies

Nature of the Residue in Animals

Ruminant Metabolism Study (Reg. Standard, 1/10/86)

The metabolism of diquat dibromide in ruminants had been extensively investigated. Ethylene bridge-labeled [^{14}C]diquat dibromide was administered at 5 ppm to a Friesian cow and two Guernsey cows using a drenching bottle. One of these Guernsey cows was additionally dosed with ethylene bridge-labeled [^{14}C]diquat dibromide at 20 ppm by the same method and with bypyridyl-labeled [^{14}C]diquat dibromide at 5 ppm; at least one month was allowed between repeat dosings. A Guernsey bull calf was also administered ethylene bridge-labeled [^{14}C]diquat dibromide at 8 ppm. The radioactivity levels in milk were found to be dose-related, and were not affected by the radiolabel position. The highest TRR in milk was 0.077 ppm and was observed in the 72-hour milk sample from the cow dosed at 20 ppm. In milk samples from the high-dose cow, residues of diquat *per se* were quantitated at <0.002 ppm (determined colorimetrically, limit of detection not provided), and did not concentrate in the fat, casein or whey. No detectable residues (<0.01 ppm) were found in the leg muscle samples from the Friesian cow dosed at 5 ppm. In the bull calf sacrificed 24 hours after dosing at 8 ppm, the TRR were 1.071 ppm in kidney, 0.033 ppm in liver and <0.04 ppm in other tissues. Residues of diquat *per se* were 0.03 ppm and <0.01 ppm in the kidney and liver samples, respectively. This study did not adequately characterize the ^{14}C-residues in the milk or tissues.

In addition to the study briefly summarized above, other cow and goat metabolism studies had been submitted but were deemed marginally adequate because the test animals were preconditioned, were not sacrificed within 24 hours of dosing, or the radioactive residues in tissues were incompletely characterized.

One of these studies in which the radioactive residues were characterized is summarized below. A lactating cow was preconditioned. Within 4 hours of the final dosing, 91 % of the cumulative

7-day dose had been eliminated from the cow in the feces and urine. Diquat per se was 96% of the radioactivity in the feces. The TRR in milk ranged from 0.0014-0.0040 ppm (approximately 0.004% of the total dose) and reached a plateau with 2-3 days of the initial dosing. Characterization of the milk TRR revealed diquat per se 13 %, diquat monopyridone 13%, and TOPPS 6%. An additional 50% was present in natural milk constituents (24%, lactose; 14%, fat; and 13%, protein). The TRR in kidney was 0.077 ppm, 0.052 ppm in liver, <0.005 ppm in muscle, and 0.002 ppm in fat. Identification was attempted only in liver and kidney due to the low TRR in muscle and fat. Diquat per se was identified as 52% of the TRR in kidney and 77% of the TRR in liver. Diquat monopyridone was identified as 14% of the residues (TRR) in kidney and 29% in liver.

Poultry Metabolism Study (J. Garbus, DEB 4716, 5/23/89)

In the poultry metabolism study, laying hens were dosed with ring-labeled [^{14}C]diquat at 32 ppm (~23x the maximum dietary burden for poultry) in the diet for 4 consecutive days. The total radioactive residues (TRR; expressed as diquat equivalents) were <0.001 ppm in egg yolks, 0.004 ppm in egg whites, 0.004 ppm in fat, 0.003 ppm in muscle, 0.042-0.058 ppm in kidney, and 0.030-0.045 ppm in liver. The predominant metabolites identified were diquat *per se* which accounted for 48% and 12% of TRR in liver and kidney, respectively; and diquat monopyridone which accounted for 4% and 15.1% of TRR in liver and kidney, respectively; diquat dipyridone and TOPPS [1,2,3,4-tetrahydro-1-oxo-pyrido(1,2-a)-5-pyrazinium salt] were additional minor (≤6.6% of TRR) metabolites identified in these poultry tissues. The unidentified radioactive residues were presumed to have been incorporated into cell constituents.

Total Radioactive Residues in Poultry Tissues After Dosing with 32 ppm ring labeled ^{14}C-Diquat.

Tissue	TRR (ppm)
Egg yolk	<0.001
Egg white	0.004
Liver	0.030-0.045
Kidney	0.042-0.058
Muscle	0.003
Fat	0.004

Identification/Characterization of Residues in Poultry Tissues

Residue	Poultry Liver	Poultry Kidney
TRR	0.030-0.045 ppm	0.042-0.058 ppm
Diquat	48%	12%
Diquat monopyridone	3.9%	15.1%
Diquat dipyridone	3.1%	6.6%
1,2,3,4-tetrahydro-1-oxo-pyrido(1,2-a)-5-pyrazinium salt (TOPPS)	1.8%	3.9%
Total Identified	56.8%	37.6%
Remainder in solvent fraction	27.1%	36.8%
Remainder in 2N HCl fraction	13.2%	23.5%
Unextracted Residue	2.6%	1.9%
Total unidentified	42.9%	62.2%

Fish Metabolism Study (C. Trichilo, Reg. Standard, 1/10/86)

In the fish metabolism study, trout and carp were exposed to an initial concentration of 1 ppm of bridge-labeled [^{14}C]diquat in the water for 7 days. The TRR (expressed as diquat equivalents) in carp head and tail, viscera, and body with skin were 0.025-0.077 ppm, 0.135-0.946 ppm, and 0.013-0.024 ppm, respectively. The TRR in skin and in flesh without skin were 0.015-0.023 ppm and 0.006-0.016 ppm, respectively. The TRR in trout head, tail, and flesh were 0.025-0.051 ppm, 0.059-0.239 ppm, and 0.008-0.01 ppm, respectively. After acid extraction and cleanup, approximately 65% of the radioactivity in carp flesh and trout viscera was identified as diquat *per se* using isotope dilution techniques.

Nature of the Residue in Plants

Potato Metabolism (R. Cook, RCB 1654, 2/25/87, MRID 40001301)

A copy of a published article "Residues in Potato Tubers Following Haulm Desiccation with ^{14}C-Diquat", Allan Edward Smith in Bulletin of Environmental Contamination and Toxicology, V.2, N.3, 1967, and also the company report and data upon which the article was based. This article had been reviewed earlier (J. Worthington, 5/14/74, PP4G1470). Both radiometric assay and chemical analysis procedures were conducted on each sample. The agreement between radiometric assay and analysis (specific for the cation) indicate no metabolism occurs in diquat. Further, radioassay for the photoproduct indicated negligible radioactivity.

The Diquat Registration Standard requested ring-^{14}C metabolism data. The registrant resubmitted the old study reviewed for the Registration Standard. The Agency generally does

not accept ^{14}C-ethylene bridge data since the reactivity of the bridge often results in scattering of ^{14}C reincorporated into a host of biologically derived compounds, obscuring metabolic pathways. However, since the study previously submitted demonstrates the negligible occurrence of the diquat photoproduct in the more polar fraction of the chemical analysis and agreement between cation assay and radioassay, the study may be considered adequate.

Rat Bioavailibility Study (D197390, F. Fort, 3/1/94)

The study was conducted according to a protocol set forth by the registrant and approved, with modifications, by CBRS and TOX. Results of the study show that diquat plant residues are largely not bioavailable (i.e. $\leq$ 5% of the ^{14}C is absorbed) as a result of feeding diquat in wheat chaff to rats. Retention of diquat residues in tissues was negligible i.e., $\leq$0.004 ppm diquat equivalents following dosing at $\geq$25X the maximum human dietary intake.

Rotational Crop Studies

The data requirements for confined rotational crops have been reviewed and deemed adequate by the Environmental Fate and Effects Division. The requirements for limited and extensive field rotational crop studies have been waived at this time.

The confined rotational crop study (Lee, 412853-01) is scientifically sound and partially fulfills the GLN165-1 (new GLN 860.1850) data requirement. This data requirement will be fulfilled by submitting another confined rotational crop study in which diquat is mixed with soil to simulate normal tillage practices. In this study, diquat was surface applied in a very thin layer of soil. EFED believes that a surface-application of an immobile herbicide (e.g., diquat) without soil incorporation simulates a no-till agricultural system. EFED believes that another confined rotational crop study is needed to simulate normal tillage conditions. Such a study requires mixing of diquat in the surface soil to maximize the contact between the herbicide and plant roots. Based on acceptable data, diquat does not appear to accumulate in mature edible plant tissue (including carrot roots, lettuce leaves, and wheat grain). In fact, the ^{14}C -diquat concentration in edible tissue was below the analytical detection limit of 8 ug kg^{-1}. In contrast, the ^{14}C-diquat concentration found in immature plants and mature nonedible plant tissues (including carrot leaves and wheat straw) was approximately 50 and 20 ug kg^{-1}, respectively. The ^{14}C-diquat found in plant tissue was attributed to surface contamination of plant material with diquat-amended soil. EFED concluded that diquat does not accumulate in mature root, leafy, and small grain crops.

In a rebuttal, to the requirement for additional data from a normal tillage practice, the registrant stated the confined crop accumulation study (MRID 41285301) was conducted with diquat incorporation in the surface 3 inches of soil. This type of application would simulate diquat use as a herbicide/desiccant with no cultivation until planting. The registrant also states that diquat is not bioavailable to plants because it strongly binds to soil; diquat is extracted from soil using a strong acid (H_2SO_4) reflux. In addition, the registrant cited plant uptake studies on diquat and paraquat (MRID 00067153 and 00067154) that show diquat was not plant available (<0.01 µg g^{-1}

and <0.10 µg g^{-1} in barley grain and straw respectively) at rates 400X the normal; and carrots contained minimal diquat residues (0.2 µg g^{-1}) at 90 and 198 kg a.i./ha.
The registrant believes the confined rotational study (MRID 41285301) and additional information on diquat plant uptake and soil binding provide evidence that diquat is not available for crop accumulation under normal tillage conditions at standard rotational intervals.

EFGWB believes the confined rotation crop study can represent a no till as well as normal agricultural tillage condition because the diquat was incorporated into the root zone of the plant. Therefore, the confined rotational crop study (MRID 41285301) provides acceptable data and completely satisfies the 165-1 data requirement.

Residue Analytical Methods

Enforcement methods: The Pesticide Analytical Manual (PAM) Vol. II. lists a spectrophotometric method, designated as Method A (also referenced as Chevron Chemical Company RM-8-7) as available for the enforcement of tolerances for residues of diquat *per se* in/on plant and in animal commodities. In this method, residues are extracted with sulfuric acid to free diquat from the bound state, absorbed on cation exchange resin, and eluted with saturated ammonium chloride. The diquat in the eluate is reduced by sodium dithionate, forming an intense green color and is measured spectrophotometrically at 337 mμ. The limit of detection is 0.01 ppm.

The registrant has proposed new enforcement methods, RM-5B-1 and RM-5C (replaces RM-5X-1), for plant and animal commodities, respectively. Both methods involve extraction of residues by acid hydrolysis, concentration, and cleanup on an ion-exchange column, reduction with sodium borohydride, selective pH partitioning, and measurement of the diquat reduction product by gas chromatography using a nitrogen/phosphorus flame ionization detector. The stated limit of detection is 0.005 ppm for RM-5B-1; the limit of detection for RM-5C is not clearly specified. Both methods have been adequately validated by the registrant; however, an independent laboratory validation must be conducted followed by validation by the Agency's Analytical Chemistry Section before they can be deemed fully adequate for enforcement purposes. Once a successful Agency method validation has been performed, these methods will be sent to FDA for inclusion in PAM Vol. II.

Data collection: Residue data submitted for tolerance reassessment were collected using the current or proposed enforcement methods. The registrant provided adequate method validation data to verify the suitability of these methods for data collection.

Multiresidue Methods

The FDA's PESTDATA dated 11/6/90 (Pam Vol. I, Appendix) indicates that recovery of diquat dibromide using Multiresidue Protocols is unlikely. The updated PESTDATA dated 08/93 does

not have an entry for diquat dibromide.

Crop Field Trials and Livestock Feeding Studies

Crop Field Trials

All submitted magnitude of the residue data for plants have been evaluated and deemed adequate assuming that diquat *per se*, is the residue of concern. However, additional data are required for sorghum forage, sorghum stover, aspirated grain fractions of sorghum, aspirated grain fractions of soybean, alfalfa forage, alfalfa hay, clover forage and clover hay. All field residue data have been re-evaluated and plant commodity tolerances reassessed for reregistration purposes.

The registered uses of diquat dibromide on potato for preplant/preemergence or for preharvest desiccation are supported by acceptable residue field data (maximum diquat residue was 0.07 ppm) reflecting maximum label rates. Sufficient data are available to ascertain that the established tolerance of 0.1 ppm in/on potato and 1 ppm for residues in processed potato waste are adequate. However, the available data indicate that the tolerance of 0.5 ppm for residues in/on processed potato should be raised to 1 ppm to reflect the higher concentration factor which occurred in processed potatoes from potato bearing measurable weathered residues in some of the submitted tests. The tolerances should be expressed in terms of potatoes, granules/flakes and potato chips. The tolerance for potato chips will remain at 0.5 ppm.

The registered uses of diquat dibromide on sorghum and soybean grown for seed as a preharvest desiccant are supported by adequate field residue data (for sorghum grain and soybean seed only) reflecting maximum label rates. As there are no established tolerances for residues of diquat in/on sorghum and soybeans, the registrant must propose tolerances on these commodities. Tolerances of 2.0 ppm and 0.2 ppm appear to be appropriate for sorghum(maximum diquat residue was 1.6 ppm) and soybeans (maximum diquat residue was 0.16 ppm), respectively. The Agency does not feel that feeding/grazing restrictions which appear on Section 3 labels for sorghum grown for seed and soybean grown for seed are practical except for soybean forage and soybean hay. Therefore, residue data must be submitted for sorghum forage, sorghum stover, aspirated grain fractions of sorghum, and the aspirated grain fractions of soybean.

The registered uses of diquat dibromide on alfalfa and clover grown for seed as a preharvest desiccant are supported by acceptable field residue data (for alfalfa seed and clover seed). The available data indicate that residues did not exceed 2.4 ppm in/on alfalfa seed and 1.7 ppm in/on clover seed following tests conducted at label rates. The registrant has proposed tolerances of 5.0 ppm for residues of diquat dibromide in/on both alfalfa and clover seed. The proposed tolerance levels appear to be too high and a new petition with lower tolerance levels is required. Tolerances of 3.0 ppm and 2.0 ppm appear to be more appropriate for alfalfa and clover seeds, respectively. Furthermore, the registrant must propose a true preharvest interval (PHI) before which seed may not be harvested, i.e., a label restriction rather than an efficacious interval. Based on the available data, a 3-day PHI would be appropriate. The Agency does not feel that

feeding/grazing restrictions which appear on Section 3 labels for alfalfa grown for seed and clover grown for seed are practical. Therefore, residue data for alfalfa forage, alfalfa hay, clover forage and clover hay are required.

The registered uses of diquat dibromide (i) as a preharvest desiccant on carrot, radish, and turnip grown for seed, and (ii) as a postharvest desiccant on cantaloupe, cucumber, pepper, squash, tomato, and watermelon are considered to be non-food uses. No residue data are required and no tolerances are needed. The raw agricultural commodities associated with these uses are not likely to be consumed by humans or animals.

As there are no registered uses of diquat dibromide on sugarcane and vetch, field residue data for these crops are no longer required. The established tolerance for residues in/on sugarcane should be revoked.

Livestock Feeding Studies

The reregistration requirements for magnitude of the residue in animals are fulfilled, provided diquat, *per se* is the residue of concern. There are no registered direct animal treatments for diquat on cattle, goats, hogs, horses, sheep, or poultry.

The maximum dietary burden for beef and dairy cattle had been calculated previously. The past dietary burden estimate was based on tolerances of commodities for which tolerances are no longer established. For reregistration purposes, a new livestock dietary burden estimate, based on reassessed established/proposed tolerances of feed commodities and revised Table 1 of OPPTS 860 Guidelines, is presented below.

Calculation of maximum ruminant dietary burden for diquat dibromide.

Commodity	Tolerance (ppm)	% Dry Matter [a]	Beef Cattle		Dairy Cattle	
			% of Diet [a]	Burden (ppm)[b]	% of Diet [a]	Burden (ppm)[b]
Soybean Seed	0.2 [c]	89	15	0.03	15	0.03
Soybean hulls	0.6 [d]	90	10	0.07	20	0.13
Potato processed waste	0.5 [f]	15	75	2.50	40	1.33

Sorghum grain	2.0 [e]	86	--	--	25	0.58
Total			100	**2.60**	100	**2.07**

[a] Table 1 (OPPTS Guideline 860.1000, August 1996).
[b] Contribution = [tolerance / % DM (if cattle)] X % diet).
[c] Recommended tolerance level for soybean seed.
[d] Recommended tolerance level for soybean hulls.
[e] Recommended tolerance level for sorghum grain.
[f] Recommended tolerance level for potato processed waste (wet peel residue levels used).

In a cattle feeding study, residues of diquat were non-detectable (<0.003 ppm) in milk and tissues following feeding of diquat-treated ryegrass silage to cattle at 3.6 ppm (~1.7x and 1.4x the maximum dietary intake for dairy and beef cattle, respectively) for 30 days. In another study, residues of diquat were nondetectable (<0.01 ppm) in milk following feeding of diquat-treated clover hay to cattle at 11 ppm (~5.3x) for 34 days. The established 0.02-ppm tolerance level for diquat residues in milk is adequate. The established tolerances of 0.02 ppm for diquat residues in the fat, meat, and meat byproducts of cattle, goats, hogs, horses, and sheep may be raised to 0.05 ppm to achieve compatibility with the Codex maximum residue limit (MRL).

The maximum dietary burden for poultry is 1.36 ppm; the calculation of the poultry burden is presented below. In a poultry feeding study, residues of diquat were mostly non-detectable (<0.005 ppm) in samples of eggs, fat, muscle, liver, and skin of chickens fed diquat at 1, 4.3, and 8.2 ppm diquat cation (~0.7x, 3.2x, and 6.0x, respectively, the estimated dietary burden) in the diet for 28 days. A single skin sample from the day-21, 8.2 ppm treatment group bore residues of 0.006 ppm. Residues in gizzard ranged from non-detectable to 0.022 ppm. The established 0.02-ppm tolerance level for diquat residues in poultry fat, meat, meat byproducts and eggs may be raised to 0.05 ppm to achieve compatibility with the Codex maximum residue limit (MRL).

Calculation of maximum poultry dietary burden for diquat dibromide.

Commodity	Tolerance	% of Diet [a]	Burden (ppm)[b]
Soybean Seed	0.2 [c]	20	0.04
Soybean hulls	0.6 [d]	20	0.12
Sorghum grain	2.0 [e]	60	1.20
Total		100	**1.36**

[a] Table 1 (OPPTS Guideline 860.1000, August 1996).
[b] Contribution = [tolerance / % DM (if cattle)] X % diet).

[c] Recommended tolerance level for soybean seed.
[d] Recommended tolerance level for soybean hulls.
[e] Recommended tolerance level for sorghum grain.

Residues in Fish

All data requirements for magnitude of the residue in fish and shellfish have been evaluated and deemed adequate to reassess the tolerances for diquat; no additional data are required regarding this topic. The available data indicate that residues of diquat in fish and shellfish will exceed the established tolerances following tests reflecting the current maximum registered use patterns. The registrant must submit a petition requesting tolerance increases from 0.1 ppm to 2.0 ppm for fish and 20 ppm for shellfish to cover all residues of diquat which may occur as a result of the currently registered uses.

Residues in Irrigated Crops

The available data concerning diquat residues following irrigation of carrot, corn (sweet), cowpea, peach, and rice are adequate to support the established 0.02 ppm tolerances for diquat residues in/on all members of the crop groups containing these commodities. However, the data also indicate that residues in/on blackberry, cowpea, orange, strawberry, mustard greens, pasture grass, and tomato may exceed the tolerances for the respective crop groups. The registrant is required to propose a higher tolerance level of 0.05 ppm for citrus fruits, small fruits, fruiting vegetables, legume vegetables, and Brassica leafy vegetables. The registrant is required to propose a higher tolerance level of 0.20 ppm for forage grasses.

No data are available for the miscellaneous commodities avocado, cottonseed, hops, and sugarcane for which tolerances currently exist. However, we will translate from data for other crops. Based on the highest residues found in other irrigated crops resulting from irrigation with water containing diquat residues, we recommend that the registrant propose tolerances of 0.20 ppm for these crops. If lower tolerances are desired, additional data will be required.

Residues in Processed Commodities

The data for magnitude of the residue in processed food/feed have been evaluated and deemed adequate to determine the extent to which residues of diquat concentrate in food/feed items upon processing of raw agricultural commodities. Acceptable potato, soybean, and sorghum processing studies have been submitted and evaluated.

The potato processing data indicate that residues of diquat concentrated 5x and 12x in potato chips and dried potato, respectively. The existing tolerance of 0.5 ppm for residues of diquat in

processed potato (which includes dried potato, granules, and chips) should be raised to 1 ppm for potato, granules/flakes. The tolerance for potato chips will remain at 0.5 ppm. Data depicting residues in dried potato processed from potato bearing measurable residues may be translated to processed potato waste. The established tolerance for residues of diquat in processed potato waste has been reassessed and found to be appropriate.

The soybean processing data indicate that residues of diquat concentrated 2.6x in soybean hulls processed from soybean bearing detectable residues. No concentration of residues was observed in other soybean processed fractions. The registrant must propose a tolerance for residues of diquat in soybean hulls; a tolerance of 0.6 ppm would be appropriate based on a recommended tolerance of 0.2 ppm for soybean and a concentration factor of ~3x in soybean hulls.

The sorghum processing data indicate that residues of diquat concentrated 4x in sorghum dry milling bran fraction processed from sorghum bearing detectable residues. According to Table 1 of OPPTS 860 Guidelines, the only processed commodity entry for sorghum is flour. Residue data are not needed for flour at this time since sorghum flour is used exclusively in the U.S. as a component for drywall, and not as either a human or animal feed item. However, because 50% of the worldwide sorghum production goes toward human consumption, the Agency reserves the right to require data if needed at a later date.

International Considerations

The residue (parent only) which is regulated presently by the U.S. is identical to the residue which is regulated by CODEX. CODEX MRLs are 0.01 ppm for milk; 0.05 ppm for eggs, maize, meat, edible offal, potato, vegetable oils (crude), and vegetables; 0.2 ppm for beans (dry), lentil (dry), peas (dry), polished rice, and soya bean (dry); 0.5 ppm for wheat flour; 1 ppm for husked rice and sunflower seed; 2 ppm for oats, rape seed, sorghum, wheat, and wheat wholemeal; 5 ppm for barley and wheat bran (unprocessed); 10 ppm for rice; 50 ppm for clover; and 100 ppm for alfalfa fodder.

Toxicology Section

Summary of Toxicological Dose and Endpoints for DIQUAT DIBROMIDE for Use in Human Risk Assessment

EXPOSURE SCENARIO	DOSE	ENDPOINT	STUDY
Acute Dietary females 13-50 years of age	none		
	Acute RfD = none		

Acute Dietary general population including infants and children	NOAEL= 75 mg/kg/day UF = 100	NOAEL = 75 mg/kg, based on clinical signs and decreased body-weight gain at the LOAEL of 150 mg/kg/day.	Acute neurotoxicity rat
	Acute RfD = 0.75 mg/kg		
Chronic Dietary	NOAEL = 0.5 mg/kg/day UF = 100	NOAEL = 0.5 mg/kg/day, based on cataracts in females and decreased adrenal and epididymides weights in males at the LOAEL of 2.5 mg/kg/day.	chronic toxicity dog
	Chronic RfD = 0.005 mg/kg/day		
Incidental Oral, Short- Term	NOAEL = 1 mg/kg/day MOE = 100	NOAEL = 1 mg/kg/day, based on decreased body-weight gain and food consumption at the LOAEL of 3 mg/kg/ day.	Developmental toxicity rabbit
Incidental Oral, Intermediate-Term	NOAEL = 0.5 mg/kg/day MOE = 100	NOAEL = 0.5 mg/kg/day, based on cataracts in females and decreased adrenal and epididymis weights at the LOAEL of 2.5 mg/kg/ day.	Chronic oral toxicity dog
Short-Term [a] [b] (Dermal)	NOAEL = 1 mg/kg/day MOE = 100	NOAEL = 1 mg/kg/day, based on decreased body-weight gain and food consumption at the LOAEL of 3 mg/kg/ day.	Developmental toxicity rabbit
Intermediate-Term [a] [b] (Dermal)	NOAEL = 0.5 mg/kg/day MOE = 100	NOAEL = 0.5 mg/kg/day, based on cataracts in females and decreased adrenal and epididymis weights at the LOAEL of 2.5 mg/kg/ day.	Chronic oral toxicity dog
Long-Term (Dermal)[a] [b]	NOAEL = 0.5 mg/kg/day MOE = 100	NOAEL = 0.5 mg/kg/day, based on cataracts in females and decreased adrenal and epididymis weights at the LOAEL of 2.5 mg/kg/ day.	Chronic oral toxicity dog
Short Term (Inhalation)	NOAEL = 0.1 μg/L MOE = 100	NOAEL = 0.1 μg/L, based on increased mean lung weight in males, mottling and reddening of lungs in females, and lung lesions [multifocal chronic interstitial pneumonia and alveolar macrophages] at the LOAEL of 0.49 μg/L.	21-day inhalation toxicity rat
Intermediate Term (Inhalation)	NOAEL = 0.1 μg/L MOE = 100	NOAEL = 0.1 μg/L, based on increased mean lung weight in males, mottling and reddening of lungs in females, and lung lesions [multifocal chronic interstitial pneumonia and alveolar macrophages] at the LOAEL of 0.49 μg/L.	21-day inhalation toxicity rat
Long Term (Inhalation)	NOAEL = 0.1 μg/L MOE = 100	NOAEL = 0.1 μg/L, based on increased mean lung weight in males, mottling and reddening of lungs in females, and lung lesions [multifocal chronic interstitial pneumonia and alveolar macrophages] at the LOAEL of 0.49 μg/L.	21-day inhalation toxicity rat

[a] A 3.3% dermal absorption factor should be used for these risk assessments. [b] Since an oral value was selected, route-to-route extrapolation should be followed.

Diquat dibromide is not acutely toxic *via* the oral [Toxicity Category III] and inhalation [Toxicity Category III] routes of exposure but is moderately-to-severely toxic *via* the dermal [Toxicity Category II] route of exposure. Diquat dibromide is not a skin irritant [Toxicity Category IV] nor a dermal sensitizer, but it is considered a moderate-to-severe eye irritant [Toxicity Category II].

Following repeat dermal exposure [5 days/week for 3 consecutive weeks], severe systemic toxicity was observed, as evidenced by high mortality and clinical signs [hypothermia, hypoactivity, dyspnea, cyanosis, pale extremities, general poor condition, and emaciated appearance]. Dermal irritation [erythema, edema, and desquamation] and tissue destruction [necrosis and eschar formation] were observed at the application site at all dose levels. Sores, severe erythema, fissures, acute necrotizing purulent dermatitis, and degeneration of the hair follicles and sebaceous glands were observed at the application site in both sexes, and congestion of the lungs, liver, and kidneys were observed in both sexes.

In a repeat dose [subchronic] inhalation study, Diquat dibromide was shown to be toxic *via* the inhalation route of exposure, as evidenced by increased lung weight, mottling and reddening of the lung, and lung lesions [multifocal chronic interstitial pneumonia and alveolar macrophages] following a 3-week exposure period.

The chronic data provide evidence that the eyes [cataracts, extralenticular lesions (vitreous adhesions, retinal detachment and synechia)] are a target organ in both the rat and dog, the adrenal and epididymides are also target organs in male dogs, and the kidney is a target organ in mice, dogs, and rabbits.

Developmental toxicity was observed in both the rat and rabbit, as evidenced by delayed skeletal ossification in the rat and an increased incidence of fetuses with friable and/or mottled livers and a higher incidence of skeletal alterations in the rabbit. Maternal toxicity was observed as decreased body-weight gain and food consumption in both the rat and rabbit. In the mouse, maternal toxicity was observed as increased incidence of deaths, clinical signs [piloerection, dyspnea, respiratory noise, abnormal posture (hunched or raised tail)], and decreased body-weight gain. Developmental toxicity was observed in the mouse, as evidenced by decreased fetal body weight and increased incidence of overall skeletal alterations.

Reproductive toxicity was observed in the rat in both generations, as evidenced by decreased numbers of live F1 pups/litter and decreased pup body-weight gain [F1 and F2]. Parental toxicity was observed as increased incidences of clinical signs [piloerection, opaque eyes, and ulcers on the palate and tongue (F1)], ophthalmoscopic signs [eye opacity, partial or total lenticular cataracts, and iritis], and decreased body-weight gains and food consumption during the premating period.

Although increased incidences of diarrhea, staining of the nose, piloerection, urinary incontinence, mouth staining, upward curvature of the spine, tip-toe gait, hunched posture, subdued behavior, and sides pinched in were observed in females following acute oral exposure in the acute neurotoxicity study, the Agency has concluded that these symptoms may not be due to direct neurotoxicity but to the general overall poor condition of the animals. Several of these and other clinical signs indicative of neurotoxicity [unsteadiness, muscular weakness, and inability to stand, hypothermia, hypoactivity, dyspnea, cyanosis, pale extremities] were observed in pregnant rats and mice after oral administration during gestation and in rats following

subchronic dermal exposure. No evidence of neurotoxicity was observed in the functional observational battery, motor activity measurement, or neurohistopathology examination in the subchronic neurotoxicity study in rats. Neuropathology was not observed in any study.

The data provided no indication of increased sensitivity of rats, mice, or rabbits to in utero and/or early postnatal exposure to Diquat dibromide. The HED HIARC determined that a developmental neurotoxicity study was not required for Diquat dibromide based on the fact that (1) there is no indication of abnormalities in the development of the fetal nervous system in prenatal developmental toxicity studies in rats, mice, and rabbits at oral dose levels that were maternally toxic, (2) there was no evidence of neuropathology in either the acute or subchronic neurotoxicity study, (3) the clinical and FOB observations in the acute neurotoxicity study, which could not be unequivocally correlated to an effect on the nervous system, were not observed in the subchronic neurotoxicity study, and (4) no neurotoxic effects were observed in the brain weights or histopathology of the nervous system in the chronic toxicity studies with Diquat dibromide in several species.

There is no evidence of endocrine disruption following exposure to Diquat dibromide.

There was no evidence of increased tumor incidence in the carcinogenicity studies in rats and mice, and Diquat dibromide was classified as a Category E [evidence of non-carcinogenicity to humans] by the Health Effects Division Reference Dose (RfD)/Peer Review Committee. The mutagenic data indicated that there is no concern for mutagenicity.

Diquat dibromide was poorly absorbed from the gastrointestinal tract following oral exposure [single and repeat], and it was excreted mainly in the feces. Only a small portion of the absorbed Diquat dibromide, which is rapidly excreted in the urine, is metabolized to monopyridone and dipyridone analogs. Diquat dibromide did not accumulate in any tissue monitored.

There are no toxicology datagaps at this time.

Residues in Water Section

Table 1: Diquat and its degradates from acceptable guideline studies.

Study	Degradates				Comments
	Major	%	Minor	%	
Hydrolysis					Diquat was stable

Aerobic soil met.					
Anaerobic soil met.					
Soil photolysis	None	0	None	0	Stable. Nothing but parent was observed in extracts, 40246101
Aqueous photolysis	**1,2,3,4-tetrahydro-1-oxopyrido (1,2-a) pyrazin-5-ium ion**	**12**	**None**		**74 day half-life. Degradate took 32 days to reach significant (>10% concentrations) Most diquat will not be in water column, and this degradate will not be present under most conditions because of light attenuation. Also, diquat dibromide is not going to be in the water column long enough to form this degradate at any significant level.**
Aerobic aquatic met.	**None**	**0**	**None**	**0**	**Stable. No volatiles or degradates detected.**
Anaerobic aquatic met.	**Unknown**	**15 %**			**Stable.** Diquat was variable, ranging from 77.5 - 103.1% of the applied), with no clear pattern of dissipation. However, there was an unidentified degradate (presumed to be one degradate) that reached up to 15 % of applied in the aquatic metabolism studies. Only one interval with >10 % degradate formed.

Table 2: Diquat and degradates from available monitoring data.

Chemical	Concentration (ppb)		comments
	Surface Water	**Groundwater**	
Diquat	No monitoring in NAWQA	No monitoring in NAWQA	Highest exposure will be from aquatic herbicide applications.

Based on its environmental fate characteristics, diquat should be persistent in soil and will be sorbed to sediment under most cases if soil erosion occurs. However, desorption from sediment may occur, and the extent of desorption will depend on the soil/sediment characteristics and the ratio of water:soil that is primarily determined by depth. EFED has no monitoring data to evaluate drinking water except for the potable water studies. Highly variable estimates of water concentrations have been observed in potable water studies. The concentrations at reservoir pumps ranged from non-detections (LOD 0.003 ppm) to 0.26 ppm, and exceeded the 0.02 ppm tolerance 16 days after water treatment.

According to the Corp of Engineers in Florida, there is a 600 ft setback distance from intakes with a 1-3 day restriction on using treated water, depending on the application rate. This is consistent with the label. Rates of 0.5 lb gal product/acre or less require a 1-day restriction, 0.75-1 gal product/acre requires a 2 day restriction, and >1 gallon require a 3-day restriction. The label also states that no more than 1/3 to ½ of a lake can be treated at once and 14 days must elapse between treatments. Posting is required at 1,600 feet downstream of treatment in flowing water and 1/4 mile from treated water in standing wate bodies.

Advantages of chemical weed control:

Aquatic herbicide application can be less expensive than other aquatic plant control methods.

Aquatic herbicides are easily applied around underwater obstructions and structures, such as docks.

Aquatic herbicides can be applied directly to problem areas of all size scales.

Disadvantages of chemical weed control:

Some herbicides have swimming, drinking, and water use restrictions. Herbicide use may have unwanted impacts to people who use the water and to the environment.

Non-targeted plants as well as nuisance plants may be adversely impacted by some herbicides.

Depending on the herbicide used, it may take several days to weeks or several treatments during a growing season before the herbicide controls or kills treated plants.

Rapid-acting herbicides like Aquathol (active ingredient Endothall) may cause low oxygen conditions to develop as plants decompose. Low oxygen conditions may result in fish kills.

To be most effective, herbicides must be applied to specific stages of the plants, (i.e. young shoots, flowering stages).

Some expertise in using herbicides is necessary in order to be successful and to avoid unwanted impacts. Therefore, permits are required for certain types of herbicides.

Many people have strong feelings against using chemicals in water. Having the public involved and educated in the treatment process is beneficial.

Some local jurisdictions have policies forbidding or discouraging the use of aquatic herbicides. As policies change, control practices must adjust.

Based on a conversation with the Corp of Engineers:

Diquat is a broad spectrum, contact herbicide (kills grass and broadleaves) that is applied to some emergent and floating vegetation in both southern, mid-Atlantic, and northern states. Diquat is used each year in aquatic weed control and most is applied in Florida where 2.5 million acres of water are managed. It kills submerged weeds with a short contact time. As a result, it is used as a spot treatment where it is impossible to use a systemic herbicide that requires a high

concentration for an extended period of time. Use of diquat to treat smaller areas prevents application of other herbicides to larger areas. Also, the expense of diquat prevents large areas of application in most cases. It is usually applied early in the growth season to smaller plants because it is only a contact herbicide, while systemic chemicals have a larger application window.

It is applied 1-3 times/year depending on the plant to be treated and the climate. There is a 10-month growth period in Florida versus about 5 months in the North. If the plant is older or the growing season is longer, diquat may need to be used more than once because it is a contact herbicide. Therefore, it is usually applied once/season in the North and possibly 2-3 times/season in Florida. Diquat is applied to small areas such as boat entrances to lakes, near docks and swimming areas, boat ramps, and boat trails. Because it is a broad spectrum herbicide, it is used to prevent treatment to larger areas with a systemic herbicide.

South

It is the only chemical that will control water lettuce, is used to control hydrilla, and is used for duckweed control (nuisance infestations only not eradication). It also fills the niche that 2,4-D or triclopyr (assuming it is registered) will not cover.

Mid-Atlantic and North

It is the only product that can be used to control Egeria, which grows in NC, VA, and CA. In the north, it is used to control milfoil as spot treatments near docks and swimming areas, boat ramps, access to lake areas, and boat trails. For small areas, diquat is better than 2,4-d because of very short contact time in small patches of weeds.

Other herbicide information

Larger areas are usually treated with a systemic herbicide–2,4-D, fluoridone, glyphosate, triclopyr

Glyphosate is used primarily late in season because it is systemic, and the plants translocate the chemical to the roots while it is recharging the roots with sugar. This kills the plant root.

Questions to the Committee

A. What are the residues of concern for diquat dibromide in plants for the tolerance expression and risk assessment?

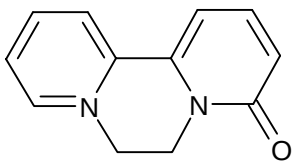
B. What are the residues of concern for diquat dibromide in animals for the tolerance

expression and risk assessment?

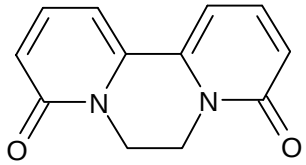
C. What are the residues of concern for diquat dibromide in water?

cc : Chem F, Chron F. Morton
RDI:Team: 8/8/01; SVH:9/13/01
TM, Thurston Morton, Rm. 816D CM2, 305-6691, mail code 7509C

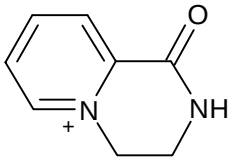
Metabolite Structures



Diquat monopyridone



Diquat dipyridone



1,2,3,4-tetrahydro-1-oxo-pyrido(1,2-a)-5-pyrazinium salt (TOPPS)